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An analysis of Y-chromosome microdeletion in infertile Korean men with severe oligozoospermia or azoospermia

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Purpose: Infertility affects 10% to 15% of couples, and male factor accounts for 50% of the cases. The relevant male genetic factors, which account for at least 15% of male infertility, include Y-chromosome microdeletions. We investigated clinical data and patterns of Y-chromosome microdeletions in Korean infertile men.

Materials and Methods: A total of 919 infertile men whose sperm concentration was ≤5 million/mL in two consecutive analyses were investigated for Y-chromosome microdeletion. Among them, 130 infertile men (14.1%) demonstrated Y-chromosome microdeletions. Medical records were retrospectively reviewed.

Results: In 130 men with Y-chromosome microdeletions, 90 (69.2%) had azoospermia and 40 (30.8%) had severe oligozoospermia. The most frequent microdeletions were in the azoospermia factor (AZF) c region (77/130, 59.2%), followed by the AZFb+c (30/130, 23.1%), AZFa (8/130, 6.2%), AZFb (7/130, 5.4%), AZFa+b+c (7/130, 5.4%), and AZFa+c (1/130, 0.7%) regions. In men with oligozoospermia, 37 (92.5%) had AZFc microdeletion. Chromosomal abnormalities were detected in 30 patients (23.1%). Higher follicle-stimulating hormone level (23.2±13.5 IU/L vs. 15.1±9.0 IU/L, p<0.001), higher luteinizing hormone level (9.7±4.6 IU/L vs. 6.0±2.2 IU/L, p<0.001), and lower testis volume (10.6±4.8 mL vs. 13.3±3.8 mL, p<0.001) were observed in azoospermia patients compared to severe oligozoospermia patients.

Conclusions: Y-chromosome microdeletion is a common genetic cause of male infertility. Therefore, Y-chromosome microdeletion test is recommended for the accurate diagnosis of men with azoospermia or severe oligozoospermia. Appropriate genetic counseling is mandatory before the use of assisted reproduction technique in men with Y-chromosome microdeletion.

Keywords: Azoospermia; Chromosomes, human, Y; Male infertility

INTRODUCTION

Infertility is a public health problem that affects about 10%–15% of couples, and male factor accounts for about 50% of the cases [1]. Many risk factors for infertility have been identified, but almost 40% of male factors for infertility are still unknown [2,3]. Genetic problems are regarded as significant factor in male infertility, and karyotype abnormalities have been found in up to 12% of patients with nonobstructive azoospermia [4]. Y-chromosome plays important roles in

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both sex determination and normal spermatogenesis. The azoospermia factor (AZF) region located on the long arm of the Y-chromosome (Yq11) is divided into three subregions: AZFa, AZFb, and AZFc. Microdeletions in the AZF region have been related to azoospermia or oligozoospermia [5]. The most common cause of male infertility is Klinefelter syndrome, and the second most common cause is Y-chromosome microdeletion [6,7]. According to the patient selection criteria, Y-chromosome microdeletion is found in about 6%–8% of men with severe oligozoospermia and 3%–15% of men with nonobstructive azoospermia [8]. Previously reported the frequencies of Y-chromosome microdeletions are slightly different between the regions which are 8.8%–10.9% in Korea [9,10], 10.8% in China [11], 14.5% in Türkiye [8], and 5.1% in Iran [12].

Recently, microdissection testicular sperm extraction and intracytoplasmic sperm injection (ICSI) have enabled patient with severe oligozoospermia or azoospermia to get successful fertilization and pregnancy [13]. However, Y-chromosome microdeletion have the risk of transmission from infertile father to their son by the procedure of ICSI. So, it is important to evaluate Y-chromosome microdeletion in men with azoospermia or severe oligozoospermia before the use of assisted reproduction technique for proper genetic counseling to patients.

The object of this study was to examine the types and frequencies of Y-chromosome microdeletions in infertile Korean men, and their relation with clinical parameters.

MATERIALS AND METHODS

Infertile men with azoospermia or severe oligozoospermia (sperm concentration ≤5 million/mL) in two consecutive semen analyses were investigated for Y-chromosome microdeletion at CHA Gangnam Medical Center from January 2015 to December 2020. Patients who underwent Y-chromosome microdeletion analysis were included, and all patients were of Korean ethnic origin. Patients with exposure to gonadotoxin (e.g., chemoradiotherapy) or testosterone replacement therapy were excluded. We analyzed personal history, physical examination, semen analyses, hormonal profiles, and chromosomal abnormalities. Their medical records were reviewed to identify the semen analysis, hormonal profiles, testis volume, and karyotype analysis retrospectively. Appropriate institutional review board approval was obtained from the CHA Gangnam Medical Center Institutional Review Board (#GCI-IRB- 2022-11-004).

Semen samples were collected into a wide-mouthed container by masturbation after 2 to 14 days of sexual abstinence. Semen samples were liquefied for at least 20 minutes at 37°C, and then semen samples were analyzed in accordance with the World Health Organization criteria. Sperm morphology was measured using Papanicolaou staining and assessed by the Kruger strict criteria. Sperm concentration and sperm motility were measured utilizing Makler counting chamber.

Serum reproductive hormones (testosterone, luteinizing hormone [LH], and follicle-stimulating hormone [FSH]) were assessed utilizing an electrochemiluminescence immunoassay analyzer (Cobas E 601, Roche). Normal reference ranges were testosterone, 2.49–8.36 ng/mL; FSH, 1.5–12.4 IU/L; LH, 1.7–8.6 IU/L.

For analysis of Y-chromosome microdeletions, genomic DNAs were extracted from peripheral blood samples using the KURABO QuickGene DNA whole blood kit S (KURABO). Eleven sequences-tagged sites on the AZF regions of the Y-chromosome—AZFa (sY84, sY86), AZFb (sY1228, sY117, sY134), and AZFc (sY152, sY157, sY158, sY1206)— were analyzed by fluorescent multiplex polymerase chain reaction (PCR). The utilized fluorescent-labeled primers are shown in Table 1. Amplification conditions of PCR were 94°C for 5 minutes, 28 cycles of 94°C for 1 minute, 61°C for 1 minute, and 72°C for 1 minute 30 seconds. The elongation was at 72°C for 30 minutes. One microliter of PCR product was mixed with formamide and Genescan™-500 LIZ™ dye Size Standard and loaded on the Genetic Analyzer 3500Dx (Thermo Fisher Scientific). The amplified products were identified using the GeneMapper 6 software (Thermo Fisher Scientific).

For karyotype analysis, conventional cytogenetic analyses were performed using a standard protocol. Phytohemagglutinin-stimulated peripheral blood cultures were carried out and GTG-banded chromosomes were analyzed using an Ikaros karyotyping system (Metasystems). For each patient, 20 metaphases were examined and karyotyped.

For statistical analysis, IBM SPSS ver. 23.0 (IBM Co.) was utilized. Student's t-test was used to compare outcomes between groups for continuous variables. p-values <0.05 were considered to be statistically significant.

RESULTS

A total of 919 infertile men were investigated for Y-chromosome microdeletion, and among them, 130 infertile men (14.1%) were found to have an AZF deletion. Ninety of 571 (15.8%) azoospermic patients and 40 of 308 (11.5%) severe oligozoospermic patients had Y-chromosome microdeletions. In patients with Y-chromosome microdeletions, 90 (69.2%) had azoospermia and 40 (30.8%) had severe oligozoospermia. The

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Table 1. Fluorescent-labeled primer sequences for Y-chromosome microdeletion analysis

STS marker	Sequence	Region	Size (bp)
GAPDH	F: FAM-ATG GGG AAG GTG AAG GTC G		107
	R: GGG TCA TTG ATG GCA ACA ATA TC		
SRY	F: FAM-AGATCCCGCTTCGGTACTCT		157
	R: GCT GTA GCG GTC CCG TTG CT		
sY117	F: FAM-GTT GGT TCC ATG CTC CAT AC	AZFb	261
	R: CAG GGA GAG AGC CTT TTA CC		
sY84	F: FAM-AGA AGG GTC TGA AAG CAG GT	AZFa	326
	R: GCC TAC TAC CTG GAG GCT TC		
sY1228	F: FAM-GCA AAG TTC TTG CAC TGT GTT T	AZFb	372
	R: GCA GGA TTA GTC AAT CAT GG		
sY1206	F: FAM-ACA GGA GGC AGA GAT TGA TC	AZFc	203
	R: GAT CAC TAC CTG TTG ACC TG		
sY134	F: FAM-GTC TGC CTC ACC ATA AAA CG	AZFb	302
	R: CCA CTG CCA AAA CTT TCA AG		
sY86	F: HEX-GTGACACACAGACTATGCTTC	AZFa	320
	R: ACACACAGAGGGACAACCCT		
sY152	F: HEX-AAGACAGTCTGCCATGTTTCA	AZFc	125
	R: ACAGGAGGGTACTTAGCAGT		
sY157	F: HEX-CTTAGGAAAAAGTGAAGCCG	AZFc	286
	R: CCTGCTGTCAGCAAGATACA		
sY158	F: HEX-CTCAGAAGTCCTCCTAATAGTTCC	AZFc	231
	R: ACAGTGGTTTGTAGCGGGTA		

STS, sequence-tagged sites; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; F, forward; R, reverse; SRY, sex-determining region Y; AZF, azoospermia factor.

Table 2. Total, azoospermia, and severe oligozoospermia number of men in complete deletion group

Complete deletion	Total (n=79)	Azoospermia (n=53)	Severe oligozoospermia (n=26)
AZFa	5 (6.3)	5 (9.4)	0 (0.0)
AZFb	5 (6.3)	5 (9.4)	0 (0.0)
AZFc	39 (49.4)	13 (24.5)	26 (100.0)
AZFa+b	0 (0.0)	0 (0.0)	0 (0.0)
AZFa+c	0 (0.0)	0 (0.0)	0 (0.0)
AZFb+c	23 (29.1)	23 (43.4)	0 (0.0)
AZFa+b+c	7 (8.9)	7 (13.2)	0 (0.0)

Values are presented as number (%).
AZF, azoospermia factor.

most frequent microdeletion was in the AZFc region (77/130, 59.2%), followed by the AZFb+c (30/130, 23.1%), AZFa (8/130, 6.2%), AZFb (7/130, 5.4%), AZFa+b+c (7/130, 5.4%), and AZFa+c (1/130, 0.7%) region. In oligozoospermic patients, the most frequent microdeletion was also in the AZFc region (37/40, 92.5%). We separately analyzed the types and incidence of Y-chromosome microdeletion as complete deletion and partial deletion, because complete deletions have prognostic value for management of patients, and partial deletions have more limited clinical value than complete deletions. Table 2 and Table 3 shows incidence of complete deletions and partial deletions, respectively.

Table 3. Total, azoospermia, and severe oligozoospermia number of men in partial deletion group

Partial deletion	Total (n=51)	Azoospermia (n=37)	Severe oligozoospermia (n=14)
AZFa	3 (5.9)	1 (2.7)	2 (14.3)
AZFb	2 (3.9)	1 (2.7)	1 (7.1)
AZFc	38 (74.5)	27 (73.0)	11 (78.6)
AZFa+b	0 (0.0)	0 (0.0)	0 (0.0)
AZFa+c	1 (2.0)	1 (2.7)	0 (0.0)
AZFb+c	7 (13.7)	7 (18.9)	0 (0.0)
AZFa+b+c	0 (0.0)	0 (0.0)	0 (0.0)

Values are presented as number (%).
AZF, azoospermia factor.

Table 4. Comparison of clinical evaluation of patients with Y-chromosome microdeletion and without any chromosomal abnormality

Parameter	No chromosomal abnormality (n=697)	Y-chromosome microdeletion (n=130)	p-value
Mean age (y)	35.4±5.2	34.8±4.6	0.264
FSH (IU/L)	18.0±12.6	20.7±12.8	0.026
LH (IU/L)	8.0±5.6	8.5±4.4	0.363
Testosterone (ng/mL)	4.0±1.6	3.7±1.3	0.012
Mean testis volume (mL)	12.8±4.3	11.4±4.6	0.001

Values are presented as mean±standard deviation.
FSH, follicle-stimulating hormone; LH, luteinizing hormone.

The 789 infertile men (85.9%, 789/919) had no Y-chromosome microdeletion, and among them 92 men (11.7%, 92/789) had karyotype abnormalities. Klinefelter's syndrome (76.1%, 70/92) was the most common karyotype abnormality. The characteristics of men with Y-chromosome microdeletion and without any chromosomal abnormality are summarized in Table 4. FSH level was significantly higher and testosterone was significantly lower in men with Y-chromosome microdeletion in comparison with men without any chromosomal abnormalities. Mean testis volume was significantly smaller in men with Y-chromosome microdeletion. However, when we analyzed clinical parameters between men without any chromosomal abnormalities and men with only Y-chromosome microdeletion (with no karyotype abnormality, n=100), there were no significantly different parameters (data not shown).

Table 5 showed the clinical characteristics of men with

severe oligozoospermia and azoospermia. FSH level and LH level were significantly higher in azoospermia compared to severe oligozoospermia. Mean testis volume was significantly smaller in azoospermia patients in comparison with severe oligozoospermia patients. No significant differences were found in testosterone level or mean age.

All patients underwent karyotyping. Karyotype abnormalities were detected in 30 patients (23.1%); of them, 28 had sex chromosome abnormalities. Table 6 shows the results of the patients' karyotypes. All patients with AZFb deletion had 46,XY karyotype, and all but one of the patients with AZFa deletion had 46,XY karyotype. All patients with AZFa+b+c deletion had abnormal karyotypes. All of three 46,XX males had AZFa+b+c deletion. Two of them were SRY (sex-determining region Y) positive and one was SRY negative.

Table 5. Clinical evaluation of patients with azoospermia and severe oligozoospermia

Parameter	Azoospermia (n=90)	Severe oligozoospermia (n=40)	p-value
Mean age (y)	34.4±3.8	35.8±6.0	0.181
FSH (IU/L)	23.2±13.5	15.1±9.0	<0.001
LH (IU/L)	9.7±4.6	6.0±2.2	<0.001
Testosterone (ng/mL)	3.5±1.3	4.0±1.1	0.058
Mean testis volume (mL)	10.6±4.8	13.3±3.8	0.001

Values are presented as mean±standard deviation.
FSH, follicle-stimulating hormone; LH, luteinizing hormone.

DISCUSSION

The present study investigated the Y-chromosome microdeletion in 919 infertile Korean men. The frequency of Y-chromosome microdeletions was 14.1% (130/919), and the most frequent microdeletion was AZFc deletion (59.2%). Among 130 Y-chromosome microdeletion cases, 30 patients (23.1%) had chromosomal abnormalities. Higher FSH level and LH level, and smaller mean testis volume were noticed in azoospermia patients compared to severe oligozoospermia patients.

The frequency of Y-chromosome microdeletion was 14.1% in our study. This finding was within the range of 5.7% to 21.0% reported in previous studies [14]. Our result was a little higher than those previously reported from Korea by Park et al. [9] (8.8%, 168/1,919) and Kim et al. [10] (10.9%, 134/1,226). Our result was similar to the frequency reported by Abur et al. [8] in Türkiye (14.5%, 189/1,300).

In our study, the most frequent microdeletion was AZFc (59.2%), followed by AZFb+c (23.1%), AZFa (6.2%), AZFb (5.4%),

Table 6. Overview of all patients karyotype details according to the nature of the Y-chromosome microdeletion in 130 Y deleted infertile men

Deletion site	Kind of karyotype		Abnormal karyotype
	Normal	Abnormal	
AZFa (n=8)	7	1	46,X,t(Y;18)(q11.22;q23)
AZFb (n=7)	7	0	-
AZFc (n=77)	70	7	46,X,del(Y)(q11.23) (n=1) 46,XY,t(13;16)(q22;q11.2) (n=1) 46,XY,var(22)? (n=1) mos 45,X[2]/46,XYqh-[98] (n=1) 47,XXY (n=2) 47,XYY (n=1)
AZFa+c (n=1)	1	0	-
AZFb+c (n=30)	15	15	46,X,?i(Y)(p10).ish idic(Y)(q11) (n=1) 45,X.ish der(14)t(Y;14) (n=1) 46,X,del(Y)(q11.2) (n=1) 46,X,del(Y)(q11.21) (n=1) 46,X,del(Y)(q11.22) (n=1) mos 45,X[20]/46,X,?del(Y)(q11.21)[80] (n=1) mos 45,X[94]/46,X,del(Y)(q11.23)[6] (n=2) mos 45,X[20]/46,X,?del(Y)(q11.21)[80] (n=1) mos 45,X[]/46,XYqh-[] (n=5) mos 46,X,inv(9)(p12q13),+r[82]/45,X,inv(9)[18] (n=1)
AZFa+b+c (n=7)	0	7	46,X,del(Y)(q11.23) (n=1) 46,XX male (n=3) mos 46,X,+mar[]/45,X[] (n=2) mos 47,XXX[2]/48,XXXX[2]/46,XX[46] male (n=1)

AZF, azoospermia factor; -, not applicable.

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AZFa+b+c (5.4%), and AZFa+c (1/130, 0.7%) deletions. This finding is similar to those reported in the previous Korean studies: Park et al. [9] found that the most frequent microdeletion was AZFc (56.6%), followed by AZFb+c (22.0%), AZFa (7.7%), AZFa+b+c (7.7%), and AZFb (5.9%). Kim et al. [10] found that the most frequent microdeletion was AZFc (51.5%), followed by AZFb+c (20.9%), AZFb (8.2%), AZFa (7.5%), and AZFa+b+c (5.2%). The most common type of Y-chromosome microdeletion was AZFc deletion in both men with azoospermia and severe oligozoospermia in our study. This result is similar to the previous reports [10,12,15]. The reason of the frequent AZFc deletion is still not clear, but it may be related with the existence of repetitive sequences in the region. It has been reported that some patients with AZFc deletion have ability to produce sperm, but some patients have no sperm in seminiferous tubules [16]. Previous studies found that in patients with isolated AZFc deletions, the success rate for retrieval of sperm during testicular sperm extraction (TESE) or testicular biopsy was 50%–56%, whereas in patients with AZFa and/or AZFb deletions, sperm was not detected by these surgical measures [17,18]. One hypothesis about this is that there is an autosomal homologue of the DAZ gene (deleted in azoospermia in the AZFc region) called DAZL (DAZ-like), which is located on chromosome 3. DAZL may play a role as a backup in AZFc, however, there was no such autosomal genes in AZFa and AZFb [19]. AZFa, AZFb, and AZFc deletions have been suggested to correlate with Sertoli cell only (SCO) syndrome, maturation arrest, and various phenotype (hypospermatogenesis or SCO syndrome), respectively. However, the association between phenotype and genotype have been difficult to derive a conclusion [20,21]. Consistent with this, AZFa, AZFb, and AZFb+c deletions were detected only in patients with azoospermia [10,12]. In our study, complete AZFa, AZFb, AZFb+c, and AZFa+b+c deletions were found only in men with azoospermia, and only complete AZFc deletions were detected in men with both azoospermia and severe oligozoospermia. AZFc deletion was found in 92.5% (37/40) in patients with severe oligozoospermia. There were two (5%) severe oligozoospermia patients with partial AZFa deletion and one (2.5%) severe oligozoospermia patient with partial AZFb deletion. Park et al. [9] also reported two patients with severe oligozoospermia who had AZFb or AZFb+c deletion. However, they didn't report whether it was partial AZF deletion or complete AZF deletion. Another study found that sperm retrieval was not successful with complete AZFa deletion, but there was report of sperm retrieval in patient with partial AZFa deletion [22]. It has been recommended that patients with AZFa and/or AZFb deletions should be counseled against undergoing sperm retrieval, while those with AZFc deletion can be expect an adequate sperm retrieval rate [23]. Thus, it seems physicians should distinguish between complete AZF deletion and partial AZF deletion to provide the patient with a full explanation such as sperm retrieval rate.

Here, we compared age, FSH, LH, serum testosterone, and testis volume between men with azoospermia and severe oligozoospermia. As shown in Table 5, detection of spermatozoa within the ejaculate was associated with FSH, LH, and testis volume but not with testosterone or age. This result is inconsistent with previous reports that testicular volume and FSH level can't predict the existence of spermatozoa in the ejaculate or the success of sperm retrieval and just indicate overall testicular function [17,24-26]. However, our result is consistent with the result of Park et al. [9] that testicular volume, FSH, and LH predicted the capability to preserve spermatogenic function to the level of detecting sperm in the ejaculate.

In our study, karyotype analysis results were available for all 130 patients with Y-chromosome microdeletions. Thirty patients (23.1%) of them had karyotype abnormalities. The prevalence of patients with karyotype abnormalities was similar to that reported by Kumtepe et al. [27] in Türkiye (21.0%), Ng et al. [28] in Hong Kong (26.3%), Totonchi et al. [12] in Iran (22.6%), and Kim et al. [10] in Korea (27.7%). Among our patients with chromosomal abnormalities, 27 had azoospermia and three had severe oligozoospermia. The karyotypes of the latter three patients were 46,X,t(Y;18)(q11.22;q23) with AZFa deletion, 46,XY,t(13;16)(q22;q11.2) with AZFc deletion, and 46,XY,var(22)? with AZFc deletion. The frequency of karyotype abnormalities was 50% (15/30) among those with AZFb+c deletion and 100% (7/7) among those with AZFa+b+c deletion in our study. All of these abnormalities were associated with the sex chromosome that were mainly 46,X,del(Y), mos 45,X[]/46,X,del(Y), or 46,XX male abnormalities. In our study, two Klinefelter's syndrome (47,XXY) patients had AZFc deletion and azoospermia. Their levels of FSH (40.5 IU/L and 39.0 IU/L) and LH (23.0 IU/L and 20.0 IU/L) were high, their testosterone levels (1.9 ng/mL and 2.3 ng/mL) were low, and they had small testis volume (3 mL and 4 mL, respectively). One patient with 47,XYY karyotype had AZFc deletion and azoospermia. Abur et al. [8] found that three infertile men with 47,XYY karyotype had severe oligozoospermia, those with 48,XXYY or 48,XXXY karyotype had azoospermia, and none had comorbid AZF microdeletions.

There are some limitations in this study. Firstly, this study was designed as retrospective study and there was a risk of bias for selection because it was not clear if all

patients with azoospermia or severe oligozoospermia were undergone chromosomal analysis. However, a risk of bias for selection could be low, because in our center, urologists usually recommended karyotype and/or Y-chromosome microdeletion analysis to those patients, and there were only a few patients who refused the tests. Secondly, although we analyzed classic AZF deletions, there was the absence of the analysis by a new nomenclature (e.g., AZFc (b2/b4), gr/gr deletion) [6].

CONCLUSIONS

This study showed that the frequency of Y-chromosome microdeletions was 14.1% in men with severe oligozoospermia or azoospermia in a Korean population. Therefore, Y-chromosome microdeletion test is suggested for the accurate diagnosis of men with azoospermia or severe oligozoospermia. And because Y-chromosome microdeletion carry the risk of transmission from infertile father to their son by assisted reproduction techniques, genetic counseling should be provided before assisted reproduction technique is used in infertile men with severe spermatogenic impairment.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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AUTHORS' CONTRIBUTIONS

Research conception and design: Tae Ho Lee and Dong Suk Kim. Data acquisition: Tae Ho Lee, Sung Han Shim, and Daeun Jeong. Statistical analysis: Seung-Hun Song and Dong Suk Kim. Data analysis and interpretation: Tae Ho Lee and Dae Keun Kim. Drafting of the manuscript: Tae Ho Lee and Dong Suk Kim. Critical revision of the manuscript: Seung-Hun Song and Dae Keun Kim. Obtaining funding: Dong Suk Kim. Approval of the final manuscript: all authors.

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